REMARKS

Entry of the foregoing and favorable reconsideration and reexamination of the subject matter pursuant to and consistent with 37 C.F.R. § 1.112 is respectfully requested.

Applicant requests consideration of these additional remarks which supplement the response file on June 29, 1999. It will be demonstrated below that the current claims of record are clearly novel and unobvious over the cited prior art of record and should be taken into consideration by the Examiner.

It should be recalled that the present claims of record are directed to a method aiming at inhibiting the replication of an immunodeficiency retrovirus wherein 100% inhibition of the retrovirus in primary cultures of monocytes in the host is achieved using selected muramyl peptides.

It should be brought to the immediate attention of the Examiner that:

(1) the claims of record encompass 100% inhibition of the retrovirus which is not disclosed in the prior art; and

(2) this inhibition was demonstrated in primary cultures (cultures prepared directly from the tissues of an organism) of monocytes of the host, which is also not demonstrated in the cited prior art.

Applicant submits that the demonstration in the present invention of 100% inhibition of a retrovirus in primary cultures of monocytes is an extremely important aspect of the present invention that must be taken into

consideration by the Examiner in analyzing the prior art. This is because it is known in the art that the use of primary cultures of monocytes is a more scientifically sound *in vitro* system for testing drugs or medicaments for the inhibition of HIV-1 than in those cell lines disclosed in the prior art, as will be discussed more extensively below under the heading HIV-1 replication.

It should be emphasized, as will be discussed in greater detail below, that the cited prior art teaches the use of muramyl peptides for inhibiting HIV-1 infection using strains that are infected by T-Tropic HIV-1 strains. The prior art is silent with respect to the use of muramyl peptides for inhibiting immunodeficiency retroviruses in the presently claimed primary cultures of monocytes which are infected by M-Tropic HIV-1 strains.

HIV-1 REPLICATION

It is now known that HIV-1 needs to replicate in macrophages or dendritic cells prior to spreading to T lymphocytes. At the early stages of HIV-1 infection, shortly after seroconversion and during the asymptomatic period of AIDS, macrophage tropic or M-Tropic strains of the virus predominate.

In contrast, in the late stages of HIV-1 disease in association with CD4 T cell decline and progression to AIDS, T cell lines or T-Tropic strains of HIV-1 predominate.

The mechanism behind entry of HIV-1 gp120 at the different stages of HIV-1 disease is different. It is now known that besides binding to the CD4 receptor, interaction of the V3 loop in gp120 with a second receptor or co-receptor is required for gp120 to enter the cells. At the early stages of HIV-1 disease the co-receptor required for the gp120 to enter the macrophages

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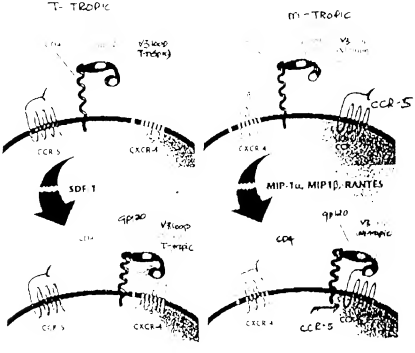
was discovered to be the CCR-5 co-receptor. In contrast, in the late stages of the disease, the co-receptor required to enter the cells was discovered to be fusin or the CXCR-4 co-receptor. These receptors are different as can be seen schematically below:

4



Both of the co-receptors were discovered to be chemokine receptors that belong to the family of G-coupled protein receptors, which have seven transmembrane regions. The fact that these receptors have seven transmembrane regions is important, since resistance to HIV-1 infection, including T cell depletion, was discovered in certain individuals bearing a mutant allele of the CCR-5 chemokine co-receptor.

This mutant CCR-5 co-receptor lacks the three transmembrane segments of the wild CCR-5 receptor and was unable to support membrane fusion by both the primary and dual-tropic virus env. Hence, it was concluded that homozygous individuals having this mutant CCR-5 receptor are highly resistant to HIV-1 infection.

The above supports the theory that the CCR-5 receptor plays a primary role in the replication of HIV-1 which replication then leads in the later stages of the disease to AIDS.

Hence, it is more scientifically beneficial to find drugs that target the early stages of HIV-1 infection using the M-Tropic HIV-1 strain at an early stage of infection, thus either diminuating or preventing the total onset of AIDS. This even the more so since macrophages serve as a reservoir for the virus and this reservoir is less sensitive to antiretroviral effects than T-lymphocytes.

Therefore, in the present invention inhibition of the replication of HIV-1, in the presently claimed process was demonstrated **in primary cultures of monocytes** (monocytes are precursors to macrophages) which cultures are the scientific tools of choice to use in drug evaluation experiments for HIV-1 inhibition, as explained above.

In contrast the **use of cell lines** to test for drugs which inhibit HIV-1 is highly artificial and drugs that can inhibit T-Tropic HIV replication are not necessarily effective against replication of M-Tropic viruses in macrophages. This has been demonstrated by the fact that SDF-1 (Stromal cell derived factor), the ligand for CXCR-4 , can inhibit virus entry into cell lines, but has absolutely no effect of preventing M-Tropic HIV-1 entry and infection in macrophages or primary T-lymphocytes.

Therefore, the fact that the Applicant has demonstrated 100% inhibition of a retrovirus in primary cultures of monocytes (M-Tropic HIV-1 strains) with the presently claimed muramyl peptides is an unexpected result which should distinguish clearly over the prior art of record where such a demonstration is not achieved. Rather the cited prior art teaches low inhibition of several muramyl peptides in cell lines which are T-Tropic strains of HIV-1.

These and other differences will be addressed in view of the issues brought to bear in the last Official Action.

35 U.S.C. §102(b)

The Examiner deems that Claims 14 to 21, 25, 26, 28 to 30 and 34 lack novelty in view of Schreck et al.

Furthermore, Claims 14 to 21, 25, 26, 28 to 30 and 34 lack novelty over Masihi et al.

Schreck et al.

Schreck et al. teach the use of muramyl peptides as **adjuvants** in potential vaccines against AIDS. By definition an adjuvant is an ingredient (as in a prescription or solution) that modifies the action of the principle ingredient. An adjuvant is not the active ingredient in a vaccine, as the skilled artisan well knows.

Furthermore, Schreck et al. disclose that it would be beneficial to select adjuvants that do not induce NF-κB activation and particularly if the

vaccines are to be aimed at treating seropositive individuals since it was believed that the **activation of NF-κB purportedly enhanced HIV-1 expression**.

In fact, MDP (thr)-GDP was found **to be the only lipophilic, nonpyrogenic adjuvant that demonstrated lack of NF-κB activation**. This teaching is apparent at page 188, 2nd column, lines 13 to 15 of Schreck et al.

Although two muramyl peptides, encompassed by the present claims were tested for NF-κB activation, it was discovered that in the human Mono-Mac-6 cell line **NF-κB activation was apparent using murabutide and muramatide as** set forth in the sentence bridging column 1 and column 2 at page 190 of Schreck et al. Therefore, murametide and murabutide do not belong to the selected category of an adjuvant that could be foreseen for use with an AIDS vaccine.

Furthermore, it is apparent that there is no experimental evidence that the muramyl peptides utilized in Schreck et al. can inhibit the replication of immunodeficiency retroviruses. Thus, a skilled artian can conclude nothing about whether the muramyl peptides in Schreck et al. have any inhibitory properties.

Therefore, Applicant submits that since Schreck et al. fails to teach the use of the claimed muramyl peptides as an active ingredient in a process to inhibit immunodeficiency retroviruses and since the claimed muramyl peptides do not fall into the category of those being sought in Schreck et al., the presently claimed invention is not anticipated by Schreck et al.

Masihi et al.

Masihi et al. disclose that muramyl dipeptide can enhance monocyte/macrophage CSF in serum and promote nonspecific resistance against a variety of microbial pathogens including HIV infection of $CD4^+$ H9 lymphocytes and U937 monocytic cells. However, this effect cannot be mediated by macrophage-CSF which itself has been shown to increase viral replication (see, Annex I, page 33, last paragraph, left column)

The Examiner refers to page 397 of Masihi et al. where murabutide was taught to be used as an **adjuvant** in human clinical trials. As discussed above, an adjuvant is solely used as a vehicle to modify the action of the active ingredient. Masihi et al. fails to teach that murabutide can be used in a process to treat immunodeficiency retroviruses directly.

Indeed, the cell lines used in the experiments in as the active ingredient in the manufacture of a medicament are H9, KE37/1 and U937 which are only infectable by T-Tropic HIV-1 strains. In contrast the present invention uses primary cultures of monocytes which are only infectable by M-Tropic HIV-1 strain. Thus, Masihi et al. disclose muramyl peptides for targeting the late stages of HIV-1, while the muramyl peptides in the process of the presently claimed invention target the early stage of HIV-1.

Therefore, in view of the above, Applicant submits that the presently claimed invention is not anticipated by Masihi et al.

35 U.S.C. §103(a)

Masihi et al.

Masihi et al. fail to teach the skilled artisan that murabutide can be used in a medicament as the active ingredient for inhibiting the replication of a retrovirus. Rather Masihi et al. teach the use of murabutide only as an adjuvant.

Furthermore, a skilled artisan would not extrapolate the results of a muramyl dipeptide disclosed in Masihi et al. to include all muramyl peptides, since as taught in Masihi et al. at page 189 under Reagents, different muramyl peptides have different properties.

Only if the Examiner deems that a skilled artisan would indeed extrapolate results from MDP to the rest of the muramyl peptides, Applicant would like to point out that Masihi et al. discloses only 67% reduction of the p24 antigen using MDP and only a 38% inhibition on day 14 using infected $CD4^+$ KE37/L lymphocytes and further teaches that 1000 μg/ml dosages were more effective.

Moreover, Figure 3 clearly demonstrates that less than 50% inhibition of p24 antigen using MDP at 1,000 μg/ml is achieved in U937 monocytic cells. **This percentage inhibition cannot be compared to the 100% inhibition achieved by the claimed muramyl compounds of the present invention**, which Applicant submits is an unexpected result.

Furthermore, Masihi et al. teach using 1000 μg/ml MDP which is an extremely high dosage and the side effects of MDP, including pyrogenecity and inflammatory reactions would be enormous at this particular dosage. This would discourage the skilled artisan to pursue a medicament using MDP.

Finally, in Masihi et al., the cell lines in which the muramyl peptides were tested for inhibition of HIV-1 are T-Tropic HIV-1 strains. Masihi et al. is silent with respect to the testing of these compounds in M-Tropic HIV-1 strains which clearly distinguishes the presently claimed invention from this reference, as discussed above.

In other words, Masihi et al. teach that MDP can inhibit HIV-1 infection in the late stages of the disease. Masihi et al. does not disclose nor demonstrate that MDP or any other muramyl peptide for that matter can target the early stages of HIV-1 infection, which is the most important stage to target.

It should be clear that silence in a reference is not a proper basis to maintain an obviousness rejection.

From the foregoing, favorable action in the form of a Notice of Allowance is respectfully requested and earnestly solicited.

If the Examiner has any questions concerning this application, he is requested to contact the undersigned at (703) 205-8000 in the Washington, D.C. area.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

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Annex I

Host factors in the pathogenesis of HIV disease

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Summary: Host factors play an important role in determining rates of disease progression in human immunodeficiency virus (HIV)-infected individuals. HIV is able to subvert the function of its host by infecting CD4+ T cells, the normal orchestrators of immune responses. Understanding the several host and pathogen factors that influence the course of HIV infection has provided new insights into the pathogenesis of HIV disease. This advance in knowledge has also led to the development of novel therapeutic strategies for intervention in HIV disease. However, caution is warranted in light of the complexities inherent in the pathogenic processes and therapeutic interventions and the uncertainty inherent in manipulating these systems.

HIV-infected long-term non-progressors represent an excellent model to study potential host factors that influence HIV disease pathogenesis. Genetic factors certainly have a major impact on the immune responses mounted by the host. In such a regard, a polymorphism in the gene for the HIV co-receptor CC chemokine receptor 5 (CCR-5), which serves as a co-receptor for macrophage (M)-tropic strains of HIV, affords a high degree of protection against HIV infection in individuals homozygous for the genetic defect and some degree of protection against rapid progression in HIV-infected heterozygotes. HIV-specific immune responses, including cytotoxic T-lymphocyte (CTL) responses and neutralizing antibody responses, also appear to play various roles in preventing rapid disease progression.

Introduction

The pathogenesis of human immunodeficiency virus (HIV) disease is complex and influenced by both viral and host factors [1]. The multifactorial nature of HIV disease pathogenesis is reflected in the highly variable rates of disease progression that are observed in individuals infected with HIV. The complexity of host factors in modulating rates of disease progression is further underscored by the observation that individuals who were apparently infected with [illegible] variant [illegible]

ies have confirmed earlier work that demonstrated high levels of viral replication throughout the course of HIV infection (7–9) and have greatly expanded our understanding of the dynamics of HIV replication in vivo. The remarkable consistency in quantitative estimates of the rate of turnover of plasma viremia raises important questions regarding the observed variations in rates of disease progression. In this regard, future studies will need to address whether the rate of viral turnover varies according to stage of disease or whether it is an intrinsic characteristic of HIV infection. In either case, it is necessary to invoke host factors in order to explain the great variability in rates of clinical disease progression.

A delicate balance among a wide array of host factors which determines the net rate of viral replication in HIV-infected individuals. Subversion of the human immune system by HIV (the infection of cells that are critical components of an intact immune system, induction of the secretion of proinflammatory cytokines, and utilization of these products of immune activation for the replicative advantage of the virus) usually tips the balance in favor of the virus. The recent discovery that certain chemokine receptors (for example, CC chemokine receptor (CCR)5, CXC chemokine receptor (CXCR)4, CCR3, CCR2b, STRL33, Bonzo, and BOB) are utilized by different strains of HIV as co-factors to gain entry into cells has greatly expanded the number of candidate host factors that may influence the pathogenesis of HIV disease (10–18). The ability of the chemokine ligands of these receptors to block HIV entry into target cells and thereby tip the balance of immune control over virus replication in favor of the host is a new concept in the field of HIV pathogenesis that has major implications for potential therapeutic intervention.

Genetic factors may determine the outcome of interactions between virus and host in several ways. First, the host's HIV-specific immune responses are constrained by the individual's major histocompatibility complex (MHC) alleles. In addition, the recently discovered genetic defect in the CCR5 gene has a major impact on susceptibility to HIV infection in individuals homozygous for the defect, and on disease progression in HIV-infected individuals heterozygous for the defect. HIV-specific cellular and humoral immune responses likely play an important role in the control of viral replication, although the precise correlates of protective immunity have not been established; however, recent studies have shown that qualitative as well as quantitative features of these immune responses may be important modulators of disease progression.

[illegible] host factors [illegible] of HIV disease should lead to the design of novel therapeutic strategies. The goal of tipping the balance in favor of [illegible] control over virus replication may appear to be simple; however, the extraordinary complexity of manipulating host factors to this end is fraught with many potential complications. The latter point is highlighted by the negative outcomes of clinical trials for bacterial sepsis that targeted molecules thought to be directly involved in the pathogenesis of sepsis (for example, lipopolysaccharide, interleukin [illegible] and tumor necrosis factor (TNF)-α) [illegible]. The need to consider therapeutic options in the context of a balance between pro- and anti-inflammatory mediators and the need to consider distal interactions in a complex pleiotropic cytokine network apply not only to sepsis (20) but to HIV disease as well.

Cytokines and HIV disease: dysregulation of cytokine production

A highly complex network of cytokines operates to regulate the immune system. This network is redundant and pleiotropic and operates in an autocrine and paracrine manner to stimulate or suppress cellular proliferation and differentiation, and to modulate immune function (21). Chronic immune activation induced by HIV infection and associated opportunistic infections results in dysregulation of the cytokine network. Many of the observed alterations in cytokine production contribute to HIV pathogenesis by further stimulating viral replication, suppressing the ability of the immune system to mount a strong antiviral response, and inducing cytokine-mediated cytopathic effects (1, 22–24).

Similar to other chronic infections, HIV infection is associated with increased expression of proinflammatory cytokines, especially during the later stages of disease (2, 6). High levels of TNF-α, IL-1β, and IL-6 are secreted by peripheral blood mononuclear cells (PBMC) (25–30) and macrophages (31–34) from HIV-infected subjects. TNF-α, IL-1β and IL-6 are also found at elevated levels in the serum (35–40), cerebrospinal fluid (41–43), and tissues (44–49). High levels of expression of these cytokines, as well as interferon (IFN)-γ (45, 47, 50), and IL-10 (47, 50), are particularly evident in lymphoid tissue, the major site of HIV replication throughout the course of disease (8, 9, 51, 52). Chronically activated and expanded CD8+ T cells (47, 53) and macrophages (22, [illegible]) are thought to be major contributors to the elevated cytokine levels observed in HIV-infected subjects.

In addition to alterations in cytokine production, [illegible] [illegible] HIV-specific [illegible] [illegible] [illegible] [illegible] PBMC [illegible] [illegible] phases of [illegible]

HIV infection [illegible] or after treatment with HIV proteins, such as envelope gp120 and Tat (24, 55–62).

Another major disruption in the cytokine pattern observed in HIV disease is a progressive loss in the ability to produce immunoregulatory cytokines such as IL-2 and IL-12 (63–66). IL-2 and IL-12 are critical for effective cell-mediated immune responses, as they stimulate proliferation and lytic activity of cytotoxic T lymphocytes (CTL) and natural killer (NK) cells. These cell-mediated immune effectors represent the primary mechanism whereby most viral infections are cleared. In addition, IL-12 is essential for stimulating the production of T helper (Th)1-type cytokines, including IL-2 and IFN-γ, that favor the development of cell-mediated immune responses (67–69). While it is clear that the Th1 limb of cellular immune responses is impaired during the course of HIV infection (65, 70–73), controversy surrounds the proposed dominance of Th2-like responses (i.e. secretion of IL-4, IL-5, and IL-10) during progression of HIV disease. Clerici et al. showed that stimulated PBMC from HIV-infected patients exhibit a preferential Th2 pattern of cytokine secretion with disease progression (65, 70, 71, 74); however, other investigators have found a skewing of the cytokine secretion pattern of T cells from HIV-infected patients toward a Th0 state (i.e. secretion of cytokines characteristic of both Th1 and Th2 patterns) rather than toward a Th2 state (47, 72, 73). In either case, the finding that HIV replication is more efficient in Th0 compared to Th1 clones (72, 75) highlights the importance of impaired Th1 responses in the pathogenesis of HIV disease (76).

Effects of cytokines on HIV replication

The effects of cytokines on HIV replication were recognized in early studies wherein activated PBMC (77), macrophages (55 [illegible]), and B cells (79) were shown to produce soluble factors that could dramatically upregulate HIV expression in acutely and chronically infected cells of the lymphocytic and macrophage lineages. These observations led to the identification of numerous cytokines that can directly influence HIV replication in infected cells (22, 24–80) (Fig. 1).

Cytokines that have been reported to upregulate HIV replication in vitro include IL-1β, IL-2, IL-3, IL-6, IL-7 (81), IL-12 (82, 83), IL-15 (82, 84), TNF-α, TNF-β, and the colony-stimulating factors (CSF) macrophage (M)-CSF and granulocyte macrophage (GM)-CSF (reviewed in (24)). IFN-α, IFN-β, and IL-16 (85, 86) are primarily suppressors of HIV production, whereas other cytokines, such as IL-4 (87), IL-10 (88, 89), IL-13 (87), IFN-γ and TGF-β reduce or enhance viral replication depending on the infected cell type and the culture conditions (22, 24, 80). Many cytokines, such as the interferons and TNF-α, can influence HIV replication in both T cells and macrophages, while others, such as M-CSF, are cell lineage-specific. The effects of a particular cytokine are often greatly influenced by the activity of other cytokines present in the microenvironment. In this regard, certain cytokines have been demonstrated to act in a synergistic (88, 90, 9[illegible]) or in an antagonistic (92, 93) manner with other cytokines in regulating HIV replication. Finally, cytokines are pleiotropic and the overall effects of a particular cytokine on HIV replication often reflect the balance of both HIV-inducing and HIV-inhibiting activities.

Proinflammatory cytokines, particularly TNF-[illegible], are considered the most potent HIV-inducing cytokines and their mechanism of action is relatively well understood. Both TNF-[illegible] and IL-1β activate the cellular transcription factor nuclear factor (NF)-κB (94, 95), a strong inducer of HIV long terminal repeat (LTR)-mediated transcription. IL-6 alone appears to upregulate HIV expression primarily by a post-transcriptional mechanism; however, IL-6 can synergize with NF-κB-inducing cytokines to enhance HIV transcription (92). The role of endogenous proinflammatory cytokines in the regulation of HIV replication has been demonstrated in several cellular systems in vitro. The production of HIV by macrophages or PBMC stimulated with [illegible] of proinflammatory [illegible] such as bacterial endotoxin or IL-2 [illegible] partially or nearly completely abrogated by the addition of anti-proinflammatory [illegible] [illegible]

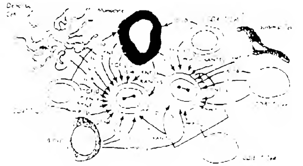


Fig. 1. Endogenous cytokines regulate viral replication in CD4+ T cells. Numerous cytokines, particularly the proinflammatory cytokines TNF-α, IL-1β and IL-6, strongly upregulate viral replication. TGF-β and IL-10 downregulate viral replication; in the case of IL-10, this effect is at least in part due to downregulation of proinflammatory cytokines. The β-chemokines, which are secreted by a variety of cells including CD8+ and CD4+ mononuclear cells, strongly inhibit infection by M-tropic strains of HIV-1, whereas SDF-1 inhibits infection with T-tropic strains. (Adapted from [illegible])

[redacted]

such as IL-1 and TNF is stimulated largely by their ability to induce the production of activity of HIV-inducing proinflammatory cytokines (92, 93, 96, 99). HIV production by infected T cells is enhanced by both the antiproinflammatory and the antiproliferation activity of such cytokines (D. Golde & A.S. Fauci, unpublished data).

Although the role of proinflammatory and antiproinflammatory cytokines in the regulation of HIV replication has not been directly investigated consistently, several lines of evidence suggest that these cytokines may be involved in regulating virus production. Administration of pentoxifylline, an inhibitor of the secretion and activity of TNF, to HIV-infected individuals was found to reduce HIV viremia in concert with a reduction in plasma levels of TNF-α (100, 101). The role of proinflammatory cytokines in maintaining steady-state levels of HIV replication is suggested by the observation that in vivo infusion of a single bolus of IL-10 to HIV-infected subjects resulted in a rapid and modest albeit transient decrease in plasma viremia (D. Weissman & A.S. Fauci, unpublished data). The kinetics of HIV suppression in vivo correlated with a dramatic reduction in the ability of cells from these subjects to be induced in vitro to secrete TNF-α and IL-1β. Furthermore, IL-10 has been found to inhibit acute HIV infection in severe combined immunodeficiency (SCID) mice engrafted with human fetal thymus and liver (102). The ability of IL-10 to suppress T-cell activation and proliferation likely also plays a prominent role in its ability to suppress HIV replication in vivo (102–105).

In addition to the use of immunosuppressive cytokines which may depress HIV-inducing immune responses, cytokines which stimulate T cells or antigen-presenting cells have been administered to HIV-infected subjects for a number of years. The use of cytokine-based therapies aimed at immune reconstitution in HIV disease has expanded over the past several years, particularly with the development of potent antiretroviral therapies that limit the potential for cytokine mediated increases in viral replication. In this regard, administration of IL-2 to asymptomatic HIV-infected subjects receiving combinant antiretroviral therapy results in significant and sustained increases in CD4+ T cell numbers with no long-term effects on viremia (106–122). Similar immune reconstitution therapies are being proposed for IL-7 (123) and IL-15 (124–126). New studies are also examining the use of these cytokines in conjunction with therapeutic vaccine regimens. A particularly interesting cytokine-based immunotherapeutic approach is suggested by a recent report demonstrating that transfection of a CD4+ T cell clone with RNA encoding the 15-kDa amino-terminal portion of IL-16 [a CD4 ligand that is a chemoattractant for CD4+ T cells (127) and a modulator of T cell activation (128–131)] results in the suppression of HIV replication in vitro (132). This effect may be due to a combination of IL-16's ability to induce T cell anergy (128, 131) and its chemoattractant activity (127). Administration of IL-2 and IL-16 to a patient with HIV infection may thus result in suppression of viral replication and expansion of CD4+ T cells. Such therapies may complement

In addition to the known cytokines mentioned previously, several soluble factors have been demonstrated to exert effects on HIV replication. The identity of the factor(s) in the putative CD8+ cell-derived HIV suppressive factor(s) (HIV-CAF) is not known. While lytic activity is an important component of CD8+ cell-mediated HIV suppression (7, 8), selective supernatants from cultures of activated CD8+ cells and CD8+ cell clones also potently inhibit HIV replication in CD4+ T cells and macrophages (7, 39). CD8 antiviral factor(s) has been described by Walker et al. (7, 8, 133). A non-cytolytic suppressor HIV replication in a non-MHC-restricted manner at the level of HIV LTR transcription (123–125) and possesses no known cytokines (126).

A distinct group of HIV-suppressive factors secreted by CD8+ T cells was identified by Cocchi et al. (127). These investigators attributed the HIV-suppressive activity of CD8+ cells to the combined activities of certain chemoattractant cytokines (i.e. chemokines), including macrophage inflammatory protein (MIP)-1α, MIP-1β and RANTES (Regulated upon Activation, Normal T cell Expressed and Secreted). An unexplained finding in the study by Cocchi et al. was that although the combination of the β chemokines MIP-1α, MIP-1β and RANTES potently suppressed the replication of several M-tropic HIV strains, they had virtually no effect on the replication of the T-cell line tropized (TCLA) strain, HIV-IIIB. Soon after this report, Feng et al. described the seven-transmembrane orphan receptor fusin previously known as LESTR and HUMSTR and currently designated CXCR-4 as a coreceptor for T-cell (2)-tropic strains of HIV (134). In addition, three groups described a new chemokine receptor, CCR5, which bound MIP-1α, MIP-1β and RANTES with a high affinity (135–137). Biological studies then revealed that CCR5 is a coreceptor for M-tropic HIV strains (138–141). The identification of HIV coreceptors has provided a new way to look at CD8 suppression as a coreceptor for M-tropic strains of HIV was isolated from [illegible] CD8+ cells [illegible] CD8+ cell-derived HIV suppressive factor [illegible] CCR5 and [illegible] CXCR-4 [illegible] MIP-1α, MIP-1β and RANTES [illegible] HIV-IIIB [illegible]

[illegible] chemokine receptor CXCR4, an interaction that is blocked by the CXCR4 ligand stromal derived factor 1 (SDF-1). Many primary T-tropic HIV isolates exhibit a broad range of CCR usage, including CXCR4 and CCR4 (132, 133). The recent discoveries of other HIV co-receptors have already made obsolete the simplistic notion that CCR5 and CXCR4 are the only important co-receptors for M- and T-tropic strains of HIV, respectively (17, 18, 134).

Numerous cell types produce a variety of chemokines (135, 136), and modulation of the production of these factors may influence HIV replication in a strain-specific manner (Fig. 1). Therefore, the overall effect of immune activation and the secretion of proinflammatory or immunoregulatory cytokines on HIV replication must now be considered in the context of potential influences on chemokine production, chemokine co-receptor expression, and the predominant viral quasispecies that is replicating in vivo. Chemokine production, induced during inflammation, is enhanced by several cytokines, including TNF-α, IL-β, and immunoregulatory cytokines, such as IL-2 and IL-15 (135, 137–139). Thus, in HIV-infected subjects in the early stages of disease, the ability of TNF-α to stimulate β-chemokine production and thereby suppress M-tropic entry may override its HIV-inducing effects. However, in individuals harboring predominantly T-tropic quasispecies in the later stages of HIV disease, only the HIV-inducing activity of TNF-α would be influential. In fact, TNF-α-mediated induction of β-chemokine secretion may actually enhance entry and replication of T-tropic strains of HIV (A. Kinter & A.S. Fauci, unpublished data) (Fig. 2).

Similarly, cytokines that modulate the expression of chemokine receptors would be expected to exert variable strain-dependent effects on HIV replication and spread. In this regard, IL-2 has been shown to upregulate the expression of the M-tropic co-receptor CCR5 (140).

The puzzling bottleneck in HIV transmission that so heavily favors emergence of M-tropic, non-syncytium-inducing (NSI) strains of virus in the new host (141, 142) may in part be due to the differential regulatory patterns of the relevant HIV co-receptors (140, 143). In this regard, CCR5 expression is predominantly seen in previously activated memory T cells (i.e. CD26^{high}CD45RA^{low}CD45RO^{+}), whereas CXCR4 expression is seen in naive, unactivated cells (i.e. CD26^{low}CD45RA^{+}CD45RO^{-}). It is therefore plausible that the profound degree of immune activation that occurs during acute HIV infection may result in high expression of CCR5 and low expression of CXCR4 (M. Ostrowski & A.S. Fauci, unpublished data). Similarly, co-infection with various other pathogens may differentially modulate expression of HIV co-receptors and thereby exert selective pressure on HIV strains that use one co-receptor or another (M. Ostrowski, M. Moriuchi, & A.S. Fauci, unpublished data).

The observation that the natural ligands of HIV chemokine co-receptors that are utilized as HIV co-receptors act as potent inhibitors of viral entry has dramatically broadened the known spectrum of HIV inhibitory cytokines and the mechanisms whereby they influence HIV replication. Therapeutic approaches currently being considered include administration of HIV-inhibitory chemokines, chemokine antagonists that occupy HIV co-receptors without inducing a signal (144), and chemokines that are highly specific for the HIV co-receptor [illegible] and [illegible] potent [illegible] [illegible] [illegible] [illegible] [illegible] [illegible]

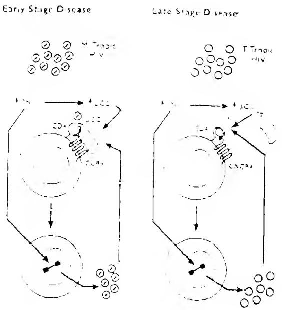


Fig. 2. Proinflammatory cytokines, such as TNF-α, have potentially dichotomous effects on HIV replication. During the early stages of HIV disease (left), M-tropic strains of the virus predominate. Although TNF-α can transcriptionally upregulate HIV expression in infected cells, at the same time it induces expression of the β-chemokines (βCC) RANTES, MIP-1α and MIP-1β. These chemokines occupy the HIV co-receptor CCR5, blocking entry of HIV into target cells. In contrast, T-tropic strains of HIV may predominate in the late stages of HIV disease (right). In this situation, the induction of βCC by TNF-α cannot block T-tropic HIV entry via CXCR4 and in fact may enhance replication of T-tropic strains of HIV.

PBMC from asymptomatic HIV-infected individuals harboring predominantly M-tropic HIV strains (144), but not to PBMC from individuals with more advanced disease harboring predominantly T-tropic HIV strains (146) (A. Kinter & A.S. Fauci, unpublished data). Similarly, HIV isolates obtained longitudinally from infected individuals with rapid disease progression exhibit reduced sensitivity to chemokines as a function of time (146, 147).

A cautionary note about these potential therapies comes from the known association of the transition from M-tropic NSI to T-tropic/syncytium-inducing (SI) viruses with disease progression. The transition from an NSI to SI virus may occur by mutation of only a few amino acid residues predominantly in the envelope V3 loop (148–155). The HIV envelope V3 loop has also been shown to be a major determinant of co-receptor usage (156). Given the error rate of viral reverse transcriptase and the rapid dynamics of viral replication, mutations in the HIV envelope gene that encode SI strains must appear very early in disease, however failure of such mutants to emerge until late in the disease process indicates a change in the selective advantage of such a mutation during the course of disease progression. Because SI variants are able to use a broader range of entry co-receptors (for example, CXCR4) compared with NSI viruses, it is possible that SI variants emerge in response to high levels of β chemokines that block cellular entry of viruses which utilize CCR5 (i.e. predominantly NSI viruses) (132, 146, 147). This potential effect of β chemokines should be investigated since the emergence of T-tropic HIV strains is associated with rapid CD4+ T cell decline and disease progression (157). Further caution is warranted in light of potential deleterious effects of the β chemokines on HIV replication in different cell types (149, 158). The situation in vivo is undoubtedly highly complex, and multiple host factors as well as regulatory aspects of co-receptor expression in different tissue compartments likely determine the environment in which selection for NSI or SI variants is made (1, 140, 159).

While in vitro culture systems and cell line models have allowed investigators to identify numerous host factors that influence HIV replication and to delineate the mechanisms whereby these factors suppress or enhance viral replication, it is difficult to anticipate how manipulation of these factors will ultimately influence HIV replication in vivo. It is clear that host factors function within the context of an interactive immune regulatory cytokine network and can have pleiotropic effects on HIV replication, some of which are viral strain specific. Nevertheless, numerous host factors have proven to be promising therapeutic targets that need to be further explored and pursued as tools for the treatment of HIV disease.

Immune activation

When one looks at the relationship between primary HIV infection and the subsequent development of AIDS, it appears that a strong prognostic indicator of the rate of disease progression is the underlying but deceptively stable viral load. High rates of virus production and clearance (approximately 10^{10} virions produced per day) are observed during primary HIV infection (158–160). Thus, even during clinically asymptomatic stages of HIV infection, persistent virus production serves as a potent source of immune activation and subsequent cytokine secretion. These cytokines in turn stimulate further viral replication.

Polyclonal activation is essential for productive HIV infection in vitro (161–163), and agents that interfere with T cell activation dramatically inhibit HIV replication in these cells (164–168). The role of immune activation in stimulating HIV replication in vivo is demonstrated by increases in viremia in HIV-infected individuals persistently or transiently exposed to exogenous immune stimuli. In this regard, HIV-infected natives of sub-Saharan Africa, who experience persistent immune activation due to chronic exposure to parasites and other pathogens, harbor high viral loads associated with rapid progression of HIV disease (165, 169). Similarly, coinfection with opportunistic pathogens, such as active tuberculosis (167–170) or pneumocystis pneumonia (171), results in dramatic increases in levels of plasma HIV viremia that return to baseline upon successful treatment of the opportunistic infection (101). The source of elevated viremia during OI was suggested by a recent study demonstrating that lymphoid tissue macrophages produce high levels of HIV in the setting of OI (172).

Confirming the role of immune activation in HIV pathogenesis are vaccination studies demonstrating that immunization of HIV-infected subjects with influenza (173) or tetanus toxoid (174) antigens results in transient but significant increases in plasma viremia. Furthermore, PBMC from HIV-infected subjects were rendered more susceptible to HIV infection in vitro following immunization with tetanus toxoid (174).

Lymphocyte co-progressors: a model to study host factors in the pathogenesis of HIV disease

mary. However, a reasonable consensus definition includes documentation of HIV infection for more than 7 years, a CD4+ T cell count greater than 600 cells/μL without significant decline over time, no symptoms of HIV-induced disease, and no history of antiretroviral therapy (184). Although a minority of cases of long-term non progressive HIV infection may be associated with attenuated strains of HIV (185–189), investigators suggest that viral attenuation is rare among long-term non-progressors, and that host factors play a dominant role in determining the state of non progression (183–184, 190–192).

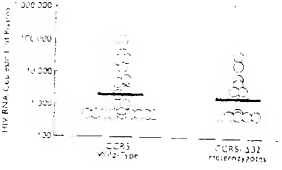


Fig. 3. Levels of plasma viremia are indistinguishable among HIV-infected long-term non-progressors stratified by CCR5 genotype. Dark bars represent median values.

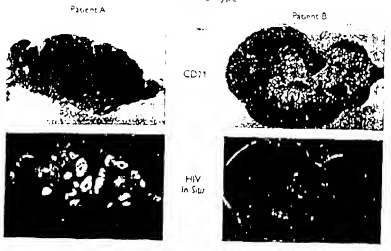
Genetic factors

Host genetic factors influence the rate of disease progression in HIV infection. A number of different mechanisms may be responsible for the observed associations between certain HLA haplotypes and different rates of HIV disease progression (193–196). The ability of certain HLA molecules to efficiently present immunodominant viral epitopes in order to generate cell-mediated immune responses may explain an association with slow disease progression. Conversely, other HLA molecules may promote immunopathogenic responses associated with more rapid disease progression. In a recent study, HLA-B27, B57, and B51 were most strongly associated with slow progression of HIV disease, while HLA-A23, B37, and B49 were associated with rapid progression (196). An HLA profile was developed that distinguished a 6-fold difference between rates of disease progression in rapid versus slow progressors. Other genetic factors linked to rates of HIV disease progression include allelic forms of the vitamin D-binding factor Gc (197), variant alleles of mannose-binding ocein (198), and the TNF-α2 microsatelite allele (199).

CCR5 is a major co-receptor for M-tropic strains of HIV-1 (above) (110–114). A mutant allele of the CCR5 gene that contains an internal 32 base pair deletion resulting in a truncated protein (200–202) has a major impact on susceptibility to HIV infection and on rates of disease progression in HIV-infected individuals. Homozygosity for the CCR5 mutation results in near total protection from HIV-1 infection (200, 202–207). Heterozygosity for the CCR5 mutation results in decreased expression of CCR5 on the cell surface and reduced infectability of CD4+ cells with M-tropic strains of HIV-1 compared to CD4+ cells from CCR5 wild-type individuals (208). Although heterozygosity for CCR5 does not appear to afford protection against HIV-1 infection, it may confer partial protection against disease progression in HIV-infected individuals (159, 202–204, 209–210). Protection against disease progression in CCR5 heterozygotes is due, in part, to lower viral [illegible] set point" after HIV seroconversion and a slower rate of CD4+ T-cell depletion compared with CCR5 wild-type individuals (204).

Heterozygosity for the CCR5 mutation is significantly more common in cohorts of HIV-infected long-term non progressors compared to HIV-infected control populations (159, 202–209, 210). However, despite the fact that the frequency of CCR5 heterozygotes is increased 2-fold among non-progressors compared to HIV-infected controls, still fewer than 50% of non progressors are CCR5 heterozygotes (202, 209). The possibility that CCR5 heterozygotes might constitute a subgroup among non-progressors with the lowest viral loads and most preserved CD4+ T cell counts was investigated. Interestingly, CCR5 wild-type and heterozygous non-progressors were indistinguishable with regard to multiple immunologic and virologic parameters of disease (e.g., CD4+ Mean CD4+ T cell counts were 9.3 cells/μL among CCR5 wild-type non-progressors and 888 cells/μL among CCR5 heterozygous non-progressors). Geometric mean levels of plasma viremia were 2,604 HIV RNA copies/ml among CCR5 wild-type non-progressors and 1,493 HIV RNA copies/ml among CCR5 heterozygotes non-progressors (209) (Fig. 3).

We have previously documented that, in contrast to individuals with progressive disease, HIV-infected long-term non-progressors maintain [illegible] (Fig. 4). However, a great deal of heterogeneity among non-progressors is evident in the degree of [illegible] demonstrated a direct correlation between [illegible] (Fig. 5).



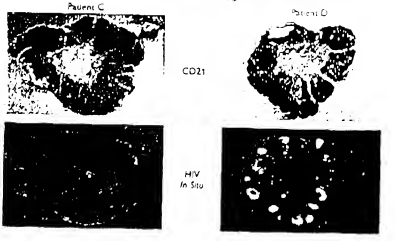


Fig. 4. The degree of follicular hyperplasia and the degree of virus trapping in lymph node germinal centers are indistinguishable among HIV-infected long-term non progressors stratified by CCR5 genotype. [illegible]

Taken together, these data indicate that although CCR5 heterozygotes have an increased chance of becoming non-progressors, HIV-infected CCR5 wild type individuals may arrive at the same non-progressive phenotype by other mechanisms.

Host immune response

CTL responses

HIV-specific CTL play an important role in the control, albeit incomplete, of HIV replication and spread (212, 213). High precursor frequencies of HIV-specific CTL with broad specificity have been consistently detected in long-term non-progressors compared to progressors (180, 214–217). Qualitative aspects of the HIV-specific CTL response are also important determinants of the efficacy of the CTL response in controlling viral replication. Vaccine-induced CTL responses specific for [illegible] progression (217, 218). This association does not appear to be due to CTL responses against autologous virus. Recognition of [illegible] CTL responses restricted by particular MHC class I alleles may result in greater anti-HIV activity (219) and may, in part, explain the association of certain MHC class I alleles with slower progression of HIV disease (220–222). Furthermore, the skewing of the T cell receptor V gene repertoire in HIV-infected patients has suggested that escape from effective HIV-specific CTL response components is heterogeneous among individuals due to primary viral sequences associated with [illegible] viral replication [illegible] progression and [illegible] in multiple individuals [illegible] (223–226). [illegible] (227–229). [illegible] CTL [illegible] (230–232). This [illegible] strategy for [illegible]

of lymphocytic choriomeningitis virus that rapidly and completely eliminate the host CTL response resulting in CTL exhaustion (i.e. high dose tolerance) (221). CTL exhaustion may occur to some degree in HIV infection where disappearance of certain originally expanded CTL clonotypes can be detected strictly in the absence of viral escape mutations that might explain the phenomenon (222).

Taken together, these observations argue against an immunopathogenic role for CTL in HIV disease (223) and in favor of a salutary role in the maintenance of low viral load and the state of non-progression. This inference is further supported by the demonstrated role of CTL in reducing levels of plasma viremia during primary HIV infection (224, 225), and the association of progression to AIDS with rare viral escape from a long-lived (9–12 years) transient dominant CTL response (226).

The host CTL response against HIV is constrained by the ability of the host's MHC class I alleles to bind to various viral epitopes, while the virus is constrained by the degree to which an escape mutation impairs viral fitness. These host-virus dynamics are extraordinarily complex given the large number of permutations of viral epitopes and MHC class I alleles. Viral mutations within CTL recognition epitopes (i.e. "escape mutants") are associated with increased levels of viral replication and progression of HIV disease (226-229). Viral escape mutants may thrive due to the release of CTL control over their replication and may also inhibit CTL responses against the prescape viral epitope (230, 231). However, certain viral escape mutations may be costly to viral fitness. In this regard, it has been reported that diffuse infiltrative CD8+ lymphocytosis in HIV infection was associated with certain HLA types that apparently constrain evolution of viral sequence diversity in the envelope V3 loop (232). Other studies have highlighted the constraints on the host CTL response imposed by MHC class I alleles. It has been reported that in an HIV-infected individual CTL clones specific for an HLA-B-8 restricted epitope of gag displayed very limited diversity of T-cell receptor utilization (233). Furthermore, limited diversity of certain CTL responses in individuals with viral escape mutants, where the dominant CTL response may remain largely directed at the pre-escape viral epitope, has been demonstrated (234, 235). The possibility that increased plasticity in the CTL response may allow the host to maintain more vigorous and effective control over viral replication was suggested by studies demonstrating increased viral sequence diversity and generation of virus-escape mutants specific for CTL responses in slow progressors (236, 237). Virus-host dynamics of CTL virus dynamics have been proposed that the rate of progression is a result of viral sequence evolution and escape on immunologically naive CTL responses and shifts the host response toward a weaker epitope (238). Thus disease progression may be the result of viral escape mutants out pacing the ability of the host CTL response. Also slow progression in HIV infection may be due to CTL plasticity overpowering viral escape mutants with limited fitness (e.g. 5).

[illegible]

Natural killer cells are activated by CD8+ T cells may also play a role in host-progression of HIV disease. It was first observed by Walker et al. (239, 240) that autologous and allogeneic-restricted, inhibitory effect replication at the level of HIV-LTR transcription (223-225) may also play an important role in disease (239). Lower CD8+ T cell levels asymptomatic patients without significant CD4+ T cell depletion were required to suppress viral replication levels compared to CD8+ T cells from patients with advanced stage HIV disease. Studies of long-term non-progressors have demonstrated more potent CD8+ T cell derived soluble antiviral responses compared with progressors (238, 240).

RANTES, MIP-1α and MIP-1β are also important antiviral soluble factors secreted by CD8+ T cells as well as other cell types (237, 241). These chemokines are natural ligands for the chemokine receptor, also known as HIV co-receptor, CCR5 and inhibit viral replication primarily at the [illegible] entry. Conflicting data have been obtained regarding a relationship between levels of these chemokines and progression of HIV disease (82, 240-243). These conflicting data are not surprising since they came from studies of viral dominant PBMC. A recent report does however support a possible role for the CC chemokines in the protection of some exposed, uninfected individuals against HIV infection (244). Consistent with HIV infection, CD8+ T cells from these individuals secreted high levels of the chemokines that were capable of preventing the replication of X4 but not R5 strains of HIV-1 [illegible]. Levels of expression of these chemokines [illegible] relevant [illegible] in vivo [illegible] in cases of slower progression [illegible]

[illegible] CD8+ cells which [illegible] CCR5 [illegible] the ligands for X4 [illegible]

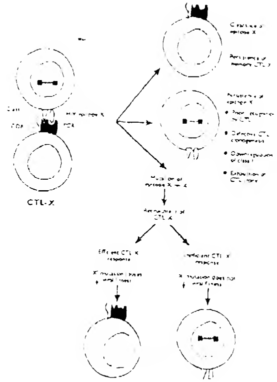


Fig. 5. The possible outcomes following CTL recognition of an HIV epitope are complex. An efficient CTL response against epitope X may result in clearance of the epitope and persistence of memory CTL (top right). Persistence of the viral epitope may be the result of a variety of factors, including poor recognition of the epitope by CTL, defective clonogenic potential of the CTL, downregulation of HLA class I molecules by viral proteins, and/or exhaustion of the CTL clone (middle right). Alternatively, a CTL escape mutation may occur in the epitope (bottom right). The outcome in this situation depends both on the relative efficiency of the CTL response directed against the escape mutant as well as on the relative cost of the mutation to viral fitness.

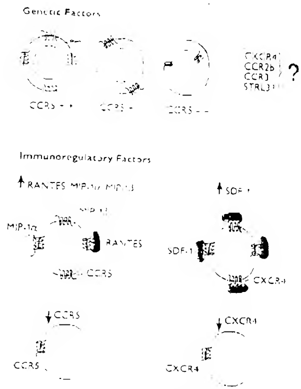


Fig. 6. Genetic as well as immunoregulatory factors govern the availability of functional HIV co-receptors. The CCR5-Δ32 allele encodes a molecule that does not function as an HIV co-receptor; individuals who are homozygous for this mutant allele are afforded near-complete protection against HIV infection, whereas heterozygotes are partially protected against disease progression. Polymorphisms in other co-receptor genes [illegible] found to correlate with [illegible] disease progression. [illegible] of the co-receptor ligands (RANTES, MIP-1α and MIP-1β in the case of CCR5 and SDF-1 in the case of CXCR4) and/or downregulation [illegible] receptors themselves may [illegible] the availability [illegible] receptors.

receptors may occur by virtue of genetic polymorphisms (i.e. CCR5 Δ32) or by downregulation of their messenger RNAs or protein products (248). Alternatively, upregulation of the natural ligands of the HIV co-receptors may prevent HIV access to functional co-receptors and thereby limit infection of target cells. However, it is important to appreciate other consequences of occupancy of HIV co-receptors by their natural ligands. As noted above, high concentrations of RANTES, MIP-1α and MIP-1β may inhibit entry and replication of M-tropic strains of HIV; however, they may also represent a selective pressure by the host immune system that may favor the emergence of T-tropic strains of HIV. Ligation of CCR5 [illegible] also [illegible] cellular signaling events that may actually enhance [illegible] of T-tropic strains of HIV (A. Kinter & A. S. Fauci, unpublished data). These possibilities [illegible] a cautionary note [illegible] strategies that [illegible] or their antagonists (244). Finally, [illegible] reported to be a [illegible] antiviral factor (249). However, [illegible] relationship between [illegible] production and disease progression [illegible] to be established (240, 245).

[illegible]

The relationship between [illegible] immune responses [illegible] disease progression [illegible] (250). [illegible] HIV [illegible] with lack of [illegible] (252) [illegible]

of neutralizing antibodies [illegible] 253). It has been reported that the presence of HIV IIIB neutralizing antibodies correlated with a more favorable prognosis (254). Subsequent studies demonstrated that the presence of neutralizing antibodies to primary HIV isolates and to autologous virus was associated with non-progression (255, 256). Furthermore, viral escape from neutralizing antibody responses is associated with emergence of the SI phenotype of HIV and with disease progression (255, 257). HIV-infected long-term non-progressors tend to maintain antibody responses that can neutralize a broad panel of primary isolates and also maintain neutralizing antibodies against autologous virus isolates, however non-progressors are a heterogeneous group with regard to these neutralizing antibody responses (253, 256). Whether the maintenance of neutralizing antibodies in non-progressors is simply a marker for a relatively intact immune system or whether these antibodies play an active role in determining the state of non-progression remains unclear.

Lymphoid tissue: substrate for immune competence

The morphologic abnormalities of lymphoid tissue associated with HIV disease progression are important determinants of immunodeficiency (8, 258-264). Despite the long period of HIV infection in long-term non-progressors, histopathologic examination of lymph node biopsies from these individuals revealed only mild HIV-related abnormalities such as follicular hyperplasia (30, [illegible]) [illegible] involution, fibrosis and lymphocyte depletion associated with progressive HIV disease were found to be lacking in lymph nodes from non-progressors. The degree of follicular hyperplasia seen in non-progressors is significantly lower [illegible] and quantitative [illegible] as well [illegible] degree of [illegible] graphic germinal centers extending into the [illegible] (20, [illegible]). It is likely that the preservation of lymphoid architecture in non-progressors is a reflection of the lower levels of viral replication over time in these individuals. Regardless of the mechanisms responsible for lower levels of viral replication in non-progressors, preservation of lymphoid tissue architecture is a critical component of the immunocompetence observed. This further highlights the need to understand the mechanisms responsible for the destruction of lymphoid architecture during progression of HIV disease. If immune-restorative strategies in advanced HIV infection are to be successful, substrate for the generation of immune responses, i.e. intact lymphoid tissue, must be present, necessitating the prevention or reversal of the histopathologic abnormalities of lymphoid tissue associated with HIV disease progression.

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